[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

Preliminary Experiments on the Synthesis of Colchicine: A Method for the Synthesis of Ring B[1]

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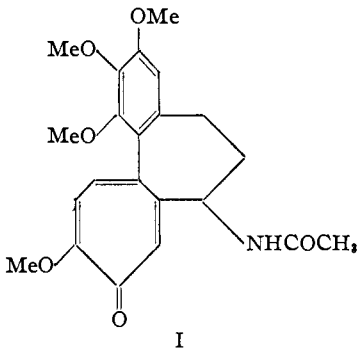
The preparation of 6,7,7a,8,9,10,11,11a-octahydro-7-N-acetylamino-5H-dibenzo[a,c]cycloheptatriene[3] (XIII), a tricyclic compound embodying the B ring structure present in colchicine, has been accomplished as follows: A Stobbe condensation between 2-phenylcyclohexanone and dimethyl succinate yielded a mixture of half esters III from which two forms (α- and β-) were isolated in pure form; reduction of the individual isomers produced three of the four theoretically possible racemates of the saturated half-ester IV (α_1, β_1 and β_2); two of the saturated half-esters (α_1 and β_1) were cyclized *via* the ester acid chloride to the ester exchange keto ester XIX *or* the desired keto ester VII depending upon the reaction conditions; the keto acid VIII was converted to XIII by hydrogenolytic removal of the keto group followed by a Curtius degradation and acetylation.

As a result of the combined efforts of a number of chemists the structure of colchicine (I) has been fairly well established,[4a] and the only remaining uncertainty concerns the possible reverse juxtaposition of the carbonyl and methoxyl groups in ring C.[4b] The conclusive proof of structure by a total synthesis, however, has yet to be achieved and thus poses an interesting preparative problem. The present communication describes some preliminary experiments directed toward this goal and demonstrates a method, worked out in a model series, for the inclusion of an acetylamino-substituted seven-membered B ring in a tricyclic structure; it is hoped that this method will prove useful in the synthesis of compounds more closely resembling colchicine.[5] The over-all synthesis starting with a 2-arylcycloalkanone, *viz.*, 2-phenylcyclohexanone (II), is detailed in the accompanying flow sheet.



I

The Stobbe Condensation with 2-Phenylcyclohexanone.[6]—2-Phenylcyclohexanone (II) underwent condensation with dimethyl succinate to furnish, in quantitative yield, a mixture of unsaturated half-esters from which a high-melting isomer (α-III) and a low-melting isomer (β-III) could be isolated in 20 and 32% yield, respectively.[7] Unsuccessful attempts were made to isolate other half-esters from the residual oil by partition chromatography of the free acid-esters on silicic acid, by chromatography of the methyl benzhydryl esters on alumina, and by chromatography of the free acid-esters on alumina. That the residual oil contained at least one other isomer, however, was indicated by the isolation of an S-benzylthiouronium salt different from that of either α- or β-III and by saponification to a dibasic acid (γ-isomer) different from those obtained from α-III and β-III. Still a fourth dibasic acid (δ-isomer) was isolated from a saponification of the crude Stobbe product and from the distilled product as described in footnote 8.

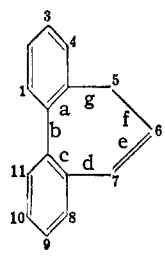
Of the three most likely structures for the unsaturated half-esters (IIIa, b, c), IIIa was considered most probable for the following reasons: (a) neither the α- nor β-isomer exhibited a strong absorption in the 250 mμ region[8] and showed only the bands associated with the phenyl ring[9]; (b) ozonolysis of β-III and saponification of the ozonolysis product yielded compounds with neutral equivalents and carbon and hydrogen analyses in accord with structures XVI and XV, respectively; (c) permanganate oxidation of both isomers yielded γ-benzoylbutyric acid (XVII) while 2-phenylcyclohexanone (*i.e.*, by oxidation of IIIc) under the same conditions yielded 2% of δ-benzoylvaleric acid but was otherwise unchanged. Although it is not surprising that the double bond assumes the endocyclic position[10] in preference to the exocyclic position, it was unexpected that it fails to become conjugated with the phenyl ring.

The structures of the dibasic acids XIV were not studied in detail. The ultraviolet spectra of the

(1) Supported in part by a grant from the National Cancer Institute, U. S. Public Health Service.

(2) du Pont predoctoral fellow, 1951–1952.

(3) The nomenclature employed in this paper for the tricyclic seven-membered B ring compounds is based on the parent structure shown at the right which is designated by *Chemical Abstracts* as 5H-dibenzo[a,c]-cycloheptatriene.



(4) (a) For review articles *cf.* J. D. Loudon, *Ann. Reports*, **45**, 190 (1948); J. W. Cook and J. D. Loudon, *Quart. Rev.*, **5**, 99 (1951); (b) For articles relating particularly to ring C *cf.* M. V. King, J. L. de Vries and R. Pepinsky, *Acta Cryst.*, **5**, 437 (1952); R. M. Horowitz and G. E. Ullyot, THIS JOURNAL, **74**, 587 (1952).

(5) N-Acetylcolchinol methyl ether, a tricyclic compound containing aromatic A and C rings and an acetylamino-substituted seven-membered B ring has been synthesized by H. Rapoport, A. R. Williams and M. E. Cisney, *ibid.*, **73**, 1414 (1951), and by J. W. Cook, J. D. Loudon, G. L. Buchanan and J. MacMillan, *J. Chem. Soc.*, 1397 (1951).

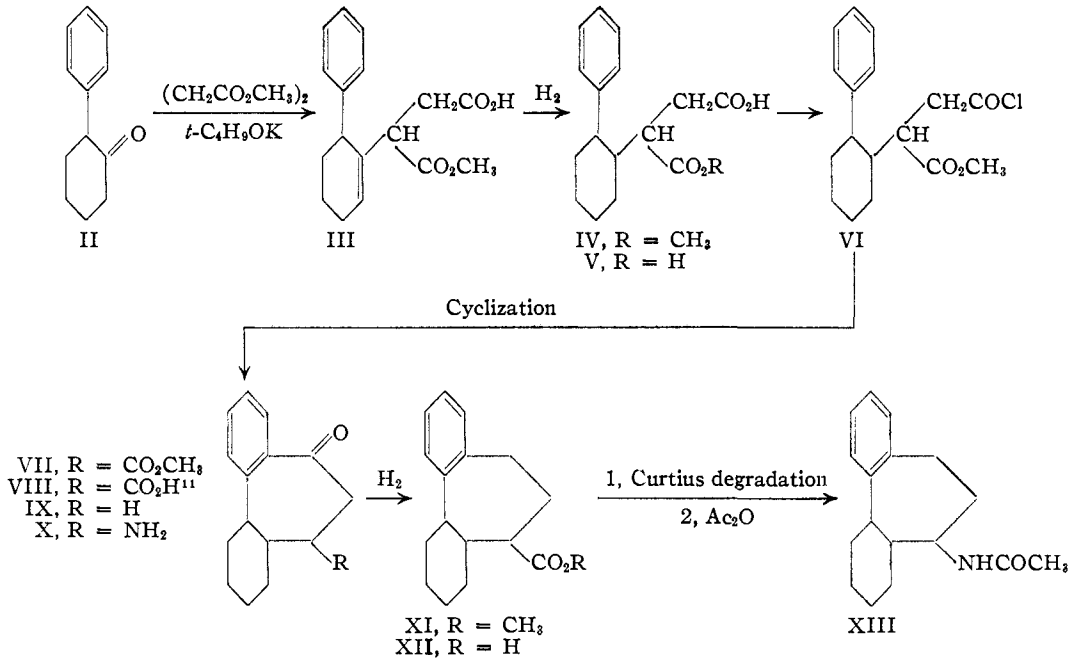
(6) For a complete survey of the Stobbe condensation *cf.* W. S. Johnson and G. H. Daub, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 1.

(7) Vacuum distillation of the crude product was accompanied by considerable decomposition and yielded a very viscous, greenish-yellow distillate from which a small amount of a dibasic acid (δ-XIV) could be isolated. Similar observations have been made by (a) J. R. Dice and G. R. Allen, Jr., THIS JOURNAL, **74**, 1231 (1952); (b) W. Cocker, B. E. Cross, A. E. Fateen, C. Lipman, E. R. Stuart, W. H. Thompson and D. R. A. Whyte, *J. Chem. Soc.*, 1781 (1950).

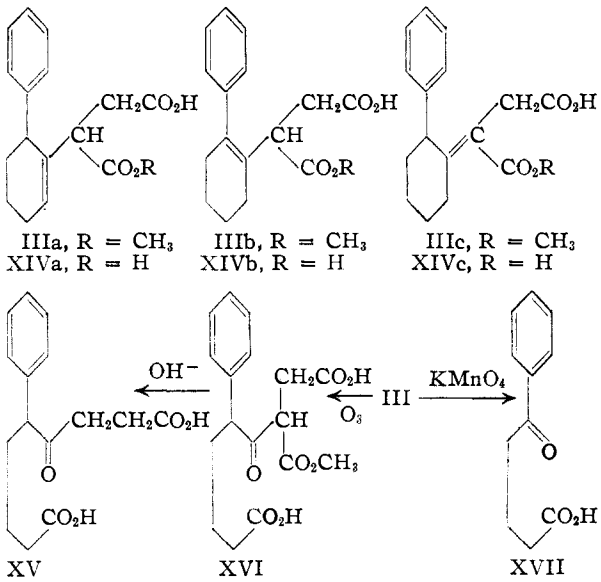
(8) 1-Phenylcyclohexane has ϵ_{max} of 6170 at 246 mμ according to M. Pestemer and L. Willigut, *Monatsh.*, **66**, 119 (1935).

(9) T. W. Campbell, S. Linden, S. Godshalk and W. G. Young, THIS JOURNAL, **69**, 880 (1947).

(10) *Cf.* W. S. Johnson, C. E. Davis, R. H. Hunt and G. Stork, *ibid.*, **70**, 3021 (1948), concerning the Stobbe condensation with cyclohexanone.



α-, β-, γ- and δ-isomers, however, rule out structure XIVb for any of these, for none showed strong absorption in the 250 mμ region.



Attempts to cyclize the unsaturated half-ester III were unsuccessful. Although neutral material could be obtained from treatment of the acid chloride of III with Lewis-acid catalysts, the ultraviolet spectrum gave no evidence for the presence of a phenyl–carbonyl link. In contrast to our results, Dice and Allen[8a] have reported the cyclization of the unsaturated Stobbe products from phenylacetone and dialkyl succinates to benzosuberone derivatives.

Reduction of the Half-ester III.—In the presence of palladium-on-charcoal catalyst, methanol and hydrogen at 2–3 atmospheres, α-III gave rise to only one isomer (α_1-IV) in 94% yield and β-III to two isomers (β_1-IV and β_2-IV) in 20–47% and 19% yield, respectively. The fourth possible racemate was not obtained. When platinum oxide was employed as the catalyst, α-III yielded, in addition to α_1-IV, 11% of a perhydro compound. Under similar conditions the δ-isomer of the dibasic acid XIV yielded 37% of a perhydro dibasic acid identical with the saponification product of the perhydro half-ester. The structure of these perhydro compounds has not been adequately established; the products fail to show a positive reaction in the Baeyer test for unsaturation[12] although the analytical data indicate an uptake of only six hydrogens. There is no doubt, however, that the phenyl ring has been at least partially reduced, for ultraviolet spectra of the perhydro compounds do not show the bands characteristic of the aromatic ring.[9]

Cyclization of the Saturated Half-ester.—To avoid ester exchange in the preparation of the acid chloride[13] the oxalyl chloride method[14] was employed. Avoidance of ester exchange in the subsequent cyclization, however, was more difficult and under most conditions a six-membered B ring compound XIX instead of the desired seven-membered B ring compound VII was obtained. Thus, aluminum chloride in nitrobenzene, aluminum chloride in anhydrous hydrogen fluoride, stannic chloride in carbon disulfide, or stannic chloride in benzene converted VI to XIX in yields of 20–84%. From the cyclization carried out with

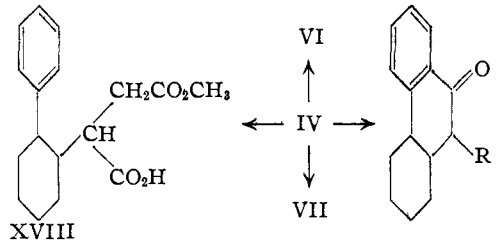
(11) To be described in detail in a later publication concerning the stereochemistry of the tricyclic ketones.

(12) In the hydrogenation studies a modified Baeyer test of increased sensitivity was employed. The compound to be tested was dissolved in one drop of 3 *N* sodium hydroxide solution and was then treated with a few ml. of saturated sodium bicarbonate solution followed by one drop of a 2% aqueous permanganate solution. Unsaturated acids which failed to give a positive test when acetone was employed as a solvent gave a rapid positive reaction under these conditions.

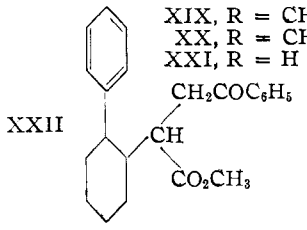
(13) For typical examples *cf.* (a) W. S. Johnson and A. Goldman, THIS JOURNAL, **67**, 430 (1945); (b) S. Ställberg-Stenhagen, *ibid.*, **69**, 2568 (1947); (c) J. Casou, *ibid.*, **69**, 1548 (1947).

(14) (a) R. Adams and L. H. Ulich, *ibid.*, **42**, 599 (1920); (b) A. L. Wilds and C. H. Shunk, *ibid.*, **70**, 2427 (1948).

stannic chloride in carbon disulfide 35% of acidic material was recovered which was neither the α_1- or β_1-half-ester IV but probably the ester exchange half-ester XVIII. A cyclization carried out with aluminum chloride in benzene solution yielded, in addition to 14% of a mixture of tricyclic ketones,



XIX, R = $CH_2CO_2CH_3$
XX, R = CH_2CO_2H
XXI, R = H



35% of the intermolecular condensation product XXII. Only with aluminum chloride in carbon disulfide did the cyclization proceed in part in the desired manner and produce a mixture containing 65% of XIX and 13% of VII. On the premise that ester exchange decreases as the catalyst activity increases, aluminum bromide in carbon disulfide was investigated and was found to bear out this prediction; from α_1-VI and β_1-VI yields of over 90% of α_1-VII and β_1-VII are obtainable. Thus, by the proper choice of catalyst and solvent the cyclization can be effected in excellent yield either *with ester exchange* to produce XIX or *without ester exchange* to produce VII. Appearing in the acidic fraction from the aluminum bromide-catalyzed cyclizations were small amounts (2–4%) of the six-membered B ring keto acids XX,[6] presumably as a result of ester cleavage by the catalyst.

The assignment of structure to the tricyclic ketones VII and XIX is based on ultraviolet absorption comparisons with a series of authentic tricyclic ketones including IX and XXI previously prepared for this purpose.[15] The close similarity between the spectra of VII and IX on the one hand and between those of XIX and XXI on the other as shown in Table I leaves little doubt as to the correctness of the assignment.

TABLE I

ULTRAVIOLET SPECTRA OF THE TRICYCLIC KETONES[a]

Compound	Size of B ring	First band λ_{max} mμ	First band ϵ_{max}	Second band λ_{max} mμ	Second band ϵ_{max}
α_1-VII	7	249	8150	285	1460
β_1-VII	7	248	7490	286	1140
IX[15]	7	249	7700	286	1540
α_1-XIX	6	249	12,100	288	1830
XXI[15]	6	249	11,780	292	1870

[a] All spectra were determined in 95% ethanol.

Synthesis of the Acetylamino Compound XIII.—The keto group of the keto acid VIII[6] was removed quantitatively by hydrogenolysis. The desoxy acid XII was converted to the acid chloride, subjected to a Curtius reaction, and the free amine so obtained was treated with acetic anhydride. The resulting product, isolated in 57% over-all yield from VIII, was the desired compound, 6,7,7a,8,9,-10,11,11a-octahydro-7-N-acetylamino-5H-dibenzo-[a,c]cycloheptatriene (XIII) embodying a B ring identical to that contained in colchicine.

Acknowledgment.—In addition to the acknowledgments to the National Cancer Institute and the du Pont Company as cited in footnotes 1 and 2 we express our thanks also to the Research Corporation for a grant which made possible the purchase of several items of equipment used in this research.

Experimental[16]

Stobbe Condensation

α-Isomer of β-Carbomethoxy-β-(2-phenylcyclohexene-6)-propionic Acid (α-III).—A slurry of 47.3 g. (0.27 mole) of 2-phenylcyclohexanone[17] (m.p. 57–58°) in 60 g. (0.41 mole) of dimethyl succinate was added to a solution of 15.7 g. (0.40 mole) of potassium in 278 ml. of dry *t*-butyl alcohol. The reaction mixture was refluxed for one hour in an atmosphere of nitrogen and was then worked up in the usual manner to yield 80.2 g. (102%) of bicarbonate-soluble material as a semi-solid mush. This material was triturated with a small amount of cold benzene, and the residue so obtained was further washed with the same solvent to leave 15.75 g. (20%) of a colorless solid, m.p. 139–141°. Two recrystallizations from aqueous ethanol gave glistening, colorless needles; m.p. 143–143.5°, λ_{max}^{EtOH} (ε) 240 mμ (159), 248 (161), 254 (191), 259 (217), 268 (136); $\lambda_{max}^{CHCl_3}$ in cm.$^{-1}$ 897, 969, 1000, 1026, 1085, 1127, 1168, 1265, 1322, 1401, 1420, 1438, 1450, 1493, 1605, 1716, 1736, 2880, 2940, 3500.[18]

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99; neut. equiv., 288.8. Found: C, 70.78; H, 6.79; neut. equiv., 287.8.

The S-benzylthiouronium salt of α-III was obtained as a white powder, m.p. 139–140°.

Anal. Calcd. for $C_{25}H_{30}N_2O_4S$: C, 66.05; H, 6.65. Found: C, 66.20; H, 6.35.

β-Isomer of β-Carbomethoxy-β-(2-phenylcyclohexene-6)-propionic Acid (β-III).—Slow evaporation of the benzene triturate described above gave a semi-crystalline mass which yielded 25 g. (32%) of a colorless solid upon trituration with solvent-D[19]; m.p. 80–84°. Three recrystallizations from this same solvent pair gave fine, microscopic needles, m.p. 90–91°; λ_{max}^{EtOH} (ε) 241 mμ (133), 248 (153), 254 (204), 260 (232), 268 (152); $\lambda_{max}^{CHCl_3}$ in cm.$^{-1}$ 895, 969, 1000, 1027, 1085, 1134, 1168, 1267, 1400, 1438, 1453, 1492, 1721, 1737, 2900, 2950, 3525.[18]

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99; neut. equiv., 288.8. Found: C, 70.61; H, 6.73; neut. equiv., 287.0.

The S-benzylthiouronium salt of β-III was obtained as a white powder, m.p. 137–138°. A mixed m.p. with the same derivative of α-III showed a depression of 5°.

Anal. Calcd. for $C_{25}H_{30}N_2O_4S$: C, 66.05; H, 6.65. Found: C, 66.00; H, 6.42.

An S-benzylthiouronium salt could be obtained from the residual oil, m.p. 128.5–129.5°.

Anal. Calcd. for $C_{25}H_{30}N_2O_4S$: C, 66.05; H, 6.65. Found: C, 66.25; H, 6.46.

(15) C. D. Gutsche, THIS JOURNAL, **73**, 786 (1951).

(16) All melting points are corrected; all boiling points are uncorrected. We are indebted for the microanalyses to Dorothy Kuenne, Patricia Clark, William Parr and James Warnhoff.

(17) M. S. Newman and M. P. Farbman, THIS JOURNAL, **66**, 1550 (1944).

(18) We are indebted to Dr. Verner L. Stromberg of the National Heart Institute, Bethesda, Md., for this infrared spectrum obtained on a Perkin-Elmer double beam instrument.

(19) "Solvent-D" will be used as an abbreviation for petroleum ether (b.p. 80–110°)-ethyl acetate(9:1) mixture—*cf.* W. S. Johnson and R. P. Graber, THIS JOURNAL, **72**, 925 (1950).

α-Isomer of the Stobbe Dibasic Acid (α-XIV).—Saponification of α-III with 5% aqueous sodium hydroxide yielded 100% of a solid, m.p. 189–191°. Two recrystallizations from aqueous ethanol produced small glistening, colorless needles, m.p. 187.5–188.5°; λ_{max}^{EtOH} (ε) 242 mμ (159), 247 (169), 253 (205), 259 (229), 264 (172). Mixed melting points with the other unsaturated acids showed marked depressions.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.11; H, 6.66.

The di-*p*-bromophenacyl derivative of α-XIV was obtained after several recrystallizations from aqueous ethanol as small needles, m.p. 146–146.5°. Mixed melting points with the same derivatives of the other unsaturated dibasic acids showed marked depressions.

Anal. Calcd. for $C_{32}H_{28}Br_2O_6$: C, 57.50; H, 4.22. Found: C, 57.30; H, 3.92.

β-Isomer of the Stobbe Dibasic Acid (β-XIV).—Saponification of β-III yielded 95% of a solid, m.p. 157–160°, which was recrystallized twice from aqueous ethanol and obtained as a white powder, m.p. 179.5–181°; λ_{max}^{EtOH} (ε) 242 mμ (137), 247 (168), 253 (214), 259 (261), 264 (188), 268 (156).

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.36; H, 6.51.

The di-*p*-bromophenacyl derivative of β-XIV was obtained as a white powder, m.p. 139–140°.

Anal. Calcd. for $C_{32}H_{28}Br_2O_6$: C, 57.50; H, 4.22. Found: C, 57.49; H, 4.10.

γ-Isomer of the Stobbe Dibasic Acid (γ-XIV).—Saponification of molecularly distilled, oily acid ester yielded, after trituration of the crude product with benzene, 81.5% of crystalline material, m.p. 164–166°. Recrystallization from aqueous ethanol gave colorless crystals, m.p. 165.5–167°; λ_{max}^{EtOH} (ε) 258 mμ (317), 268 (176).

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.00; H, 6.32.

The di-*o*-bromophenacyl derivative of γ-XIV was obtained as a white powder, m.p. 128–129°.

Anal. Calcd. for $C_{32}H_{28}Br_2O_6$: C, 57.50; H, 4.22. Found: C, 57.35; H, 4.27.

δ-Isomer of the Stobbe Dibasic Acid (δ-XIV).—Saponification of crude Stobbe half-ester with aqueous alcoholic sodium hydroxide (20%) produced 50% of a solid, m.p. 176–178°, which after two recrystallizations from aqueous ethanol existed as thin, colorless needles, m.p. 178–180°; λ_{max}^{EtOH} (ε) 251 mμ (441), 258 (336), 264 (221), 268 (179). A mixed m.p. with β-XIV was 163–170°.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61; neut. equiv., 137. Found: C, 70.05; H, 6.50; neut. equiv., 137.

Ozonolysis of β-III.—An ice-cold solution of 5.00 g. (0.017 mole) of β-III (m.p. 89–90°) in 70 ml. of dry chloroform was treated for 2 hours with oxygen containing 2.5% ozone. The ozonide was then decomposed with zinc and glacial acetic acid[20] to yield 6.3 g. of an acidic oil. Trituration with solvent-D[19] left 0.5 g. of solid, m.p. 119–123°, which after three recrystallizations from the same solvent existed as microscopic needles, m.p. 132–134°. The analytical data are in accord with **3-carbomethoxy-4-keto-5-phenylazelaic acid (XVI).**

Anal. Calcd. for $C_{17}H_{20}O_7$. C, 60.71; H, 5.99; neut. equiv., 168. Found: C, 60.82; H, 6.02; neut. equiv., 173.

The filtrates from the purification of XVI were concentrated and saponified with aqueous alcoholic sodium hydroxide (10%) to yield 95% of acidic material; m.p. 113–115°. Purification by recrystallization from solvent-D[19] gave glistening white needles, m.p. 126.5–127.5°. The analytical data are in accord with **4-keto-5-phenylazelaic acid (XV).**

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52; neut. equiv., 139. Found: C, 64.90; H, 6.54; neut. equiv., 139.

Oxidation of β-III.—Following the directions of Johnson,[10] a 5.0-g. (0.017 mole) sample of β-III (m.p. 89–90°) was oxidized at 0° with 9.16 g. (0.058 mole) of potassium permanganate and 2.76 g. (0.026 mole) of sodium carbonate in 800 ml. of water. The product consisted of 0.5 g. of a neutral fraction which yielded no carbonyl derivatives and 2.6 g. of a semi-solid acidic fraction. Trituration of the latter with solvent-D[19] yielded 0.55 g. (16%) of solid, m.p. 121.5–124.5°, which was obtained after further recrystallization from aqueous ethanol as very thin, flaky blades, m.p. 127.5–129.5°; λ_{max}^{EtOH} (ε) 242 mμ (12,200), 280 (1180). A mixed m.p. with authentic γ-benzoylbutyric acid showed no depression.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29; neut. equiv., 191. Found: C, 68.66; H, 6.28; neut. equiv., 190.

Oxidation of α-III.—From 2.5 g. of α-III (m.p. 141–142°) oxidized in the manner described above there was obtained 0.3 g. of neutral oil and 1.46 g. of a mushy, acidic solid. Purification of the latter produced 0.11 g. (6.5%) of γ-benzoylbutyric acid, m.p. 126.5–128°.

Oxidation of 2-Phenylcyclohexanone.—The oxidation of 2.5 g. (0.0144 mole) of 2-phenylcyclohexanone (m.p. 59–60°) was carried out under conditions identical to those employed for the oxidation of the half-esters. In the neutral fraction there was recovered 2.34 g. (94%) of 2-phenylcyclohexanone, m.p. 57.5–59.5°, and from the acidic portion there was isolated 0.05 g. of δ-benzoylvaleric acid, m.p. 77–78.5°. A mixed m.p. with authentic material showed no depression.

Reduction of the Stobbe Half Esters

α_1-Isomer of β-Carbomethoxy-β-(2-phenylcyclohexane)-propionic Acid (α_1-IV).—A solution of 12.66 g. of α-III (m.p. 141–142°) in 300 ml. of absolute methanol was hydrogenated at 2–3 atmospheres for 24 hours in the presence of 7 g. of 10% palladium-on-charcoal catalyst to yield 12.5 g. of an oily solid. Three recrystallizations from solvent-D[19] yielded 9.52 g. in the first crop and 2.4 g. in the second crop (total yield 94%), m.p. 151–152°; λ_{max}^{EtOH} (ε) 244 mμ (107), 249 (147), 254 (192), 259 (217), 264 (160), 268 (136); $\lambda_{max}^{CHCl_3}$ in cm.$^{-1}$ 962, 992, 1028, 1083, 1131, 1170, 1269, 1308, 1439, 1448, 1490, 1724, 1734, 2880, 2940, 3070.[18]

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.57; H, 7.37.

The S-benzylthiouronium salt of α_1-IV was obtained as a white powder, m.p. 147.5–148.5°.

Anal. Calcd. for $C_{25}H_{32}N_2O_4S$: C, 65.76; H, 7.06. Found: C, 65.61; H, 6.79.

β_1-Isomer of β-Carbomethoxy-β-(2-phenylcyclohexane)-propionic Acid (β_1-IV).—A 5.0-g. sample of β-III (m.p. 88–90°) was hydrogenated as described above to yield 4.85 g. of an oily product. Trituration with solvent-D[19] gave 4.13 g. of a solid, m.p. 100–105°, which after nine recrystallizations from the same solvent produced 1.02 g. (20% over-all) of microscopic needles, m.p. 127°; λ_{max}^{EtOH} (ε) 243 mμ (118), 249 (149), 253 (189), 259 (206), 268 (127); $\lambda_{max}^{CHCl_3}$ in cm.$^{-1}$ 952, 988, 1036, 1068, 1119, 1166, 1265, 1282, 1325, 1385, 1406, 1438, 1446, 1492, 1719, 1736, 2880, 2950, 3080.[18]

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.18; H, 7.46.

The S-benzylthiouronium salt of β_1-IV was obtained as a white powder, m.p. 139–140°.

Anal. Calcd. for $C_{25}H_{32}N_2O_4S$: C, 65.76; H, 7.06. Found: C, 65.47; H, 6.92.

β_2-Isomer of β-Carbomethoxy-β-(2-phenylcyclohexane)-propionic Acid (β_2-IV).—The combined filtrates from the purification of β_1-IV (*cf.* above) were concentrated to yield 1.43 g. of solid, m.p. 104–106°. Two recrystallizations yielded 0.98 g. (19% over-all) of extremely fine, microscopic needles, m.p. 104.5–106°; λ_{max}^{EtOH} (ε) 248 mμ (125), 253 (175), 259 (202), 263 (153), 268 (124).

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.03; H, 7.42.

The S-benzylthiouronium salt of β_2-IV was obtained as a white powder, m.p. 144.5–145.5°.

Anal. Calcd. for $C_{25}H_{32}N_2O_4S$: C, 65.76; H, 7.06. Found: C, 65.91; H, 7.33.

The perhydro half-ester was obtained when a solution of 2.72 g. of α-III in 100 ml. of absolute methanol was treated with 0.5 g of platinum oxide and hydrogenated under the conditions described above. One recrystallization of the crude product from solvent-D[19] yielded 1.95 g. (71%) of solid, m.p. 126–128°. Further recrystallizations resulted

(20) A. L. Henne and P. Hill, THIS JOURNAL, **65**, 752 (1943).

in two fractions: 25% of α_1-IV and 11% of a perhydro compound as elongated, microscopic blades, m.p. 128.5–129°.

Anal. Calcd. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.20; H, 8.72.

The perhydro dibasic acid was obtained by saponification of the perhydro half-ester described above and by platinum oxide-catalyzed hydrogenation of the δ-isomer of the unsaturated dibasic acid (δ-XIV) as colorless needles after recrystallization from aqueous ethanol, m.p. 200–201°.

Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63; neut. equiv., 140. Found: C, 68.52; H, 8.59; neut. equiv., 140.

The di-*p*-bromophenacyl derivative of the perhydro dibasic acid was obtained as colorless crystals after several recrystallizations from aqueous ethanol, m.p. 156.5–157.5°.

Anal. Calcd. for $C_{32}H_{34}Br_2O_6$: C, 56.98; H, 5.08. Found: C, 57.04; H, 5.07.

α_1-Isomer of β-Carboxy-β-(2-phenylcyclohexane)-propionic Acid (α_1-V).—Saponification of α_1-IV yielded 86% of a solid, m.p. 189–191°. Recrystallization from aqueous ethanol gave extremely fine needles, m.p. 191–192°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.79; H, 7.11.

The di-*p*-bromophenacyl derivative of α_1-V was obtained as thin blades after recrystallization from aqueous ethanol, m.p. 140.5–141.5°.

Anal. Calcd. for $C_{32}H_{30}Br_2O_6$: C, 57.33; H, 4.51. Found: C, 57.41; H, 4.39.

β_1-Isomer of β-Carboxy-β-(2-phenylcyclohexane)-propionic Acid (β_1-V).—Saponification of β_1-IV yielded 98% of solid, m.p. 186–190°, which after four recrystallizations from aqueous ethanol, existed as glistening long needles, m.p. 197–199°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.28; H, 7.22.

The di-*p*-bromophenacyl derivative of β_1-V was obtained as colorless crystals after two recrystallizations from solvent-D[19], m.p. 179–181°.

Anal. Calcd. for $C_{32}H_{30}Br_2O_6$: C, 57.33; H, 4.51. Found: C, 57.58; H, 4.68.

β_2-Isomer of β-Carboxy-β-(2-phenylcyclohexane)-propionic Acid (β_2-V).—Saponification of β_2-IV yielded 100% of a solid, m.p. 174–176°, which after three recrystallizations from solvent-D[19] existed as glistening, microscopic needles, m.p. 178–179°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.47; H, 7.03

The di-*p*-bromophenacyl derivative of β_2-V was obtained as colorless crystals after three recrystallizations from petroleum ether (b.p. 63–69°)–benzene; m.p. 174–176°.

Anal. Calcd. for $C_{32}H_{30}Br_2O_6$: C, 57.33; H, 4.51. Found: C, 57.52; H, 4.60.

Mixed melting points of the dibasic acids and of the di-*p*-bromophenacyl derivatives all showed depressions in m.p.

Cyclization of the Saturated Half-ester

α_1-Isomer of 6,7,7a,8,9,10,11,11a-Octahydro-7-carbomethoxy-5-keto-5H-dibenzo[a,c]cycloheptatriene (α_1-VII).—A 1.5-g. (0.0052 mole) sample of the α_1-saturated half-ester (α_1-IV) (m.p. 151–152°) was converted to the acid chloride by the oxalyl chloride method following the directions of Wilds and Shunk.[14b] The crude acid chloride[21] was then dissolved in carbon disulfide, filtered through a cotton plug into an addition funnel, and added dropwise at room temperature over a period of 15 minutes to a stirred solution of 4 g. (0.015 mole) of anhydrous aluminum bromide in 80 ml. of carbon disulfide. After stirring for an additional 4 hours, the reaction mixture was hydrolyzed and processed in the usual fashion to yield 0.03 g. (2%) of solid, bicarbonate-soluble material and 1.16 g. (96%) of neutral material. The acidic fraction was recrystallized from aqueous ethanol and was obtained as colorless crystals, m.p. 176–177.5°, which did not depress the m.p. of α_1-XX[6] upon admixture. The neutral fraction, m.p. 154–157°, was recrystallized three times from ethanol and obtained as 0.90 g. (75%) of thick, colorless blades, m.p. 157–157.5°; $\lambda_{max}^{CHCl_3}$ in cm.$^{-1}$ 853, 866, 888, 914, 944, 956, 988, 1021, 1048, 1077, 1105, 1125, 1145, 1170, 1235, 1270, 1298, 1319, 1350, 1365, 1420, 1445, 1455, 1480, 1605, 1680, 1720, 2820, 2910, 3000.[22]

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.09; H, 7.19.

The semicarbazone of α_1-VII was obtained after three recrystallizations from aqueous ethanol as small needles, m.p. 215–217° (dec.), λ_{max}^{EtOH} 260 mμ, ϵ 17,000.

Anal. Calcd. for $C_{17}H_{23}N_3O_3$: C, 65.63; H, 7.04. Found: C, 65.56; H, 6.85.

β_1-Isomer of 6,7,7a,8,9,10,11,11a-Octahydro-7-carbomethoxy-5-keto-5H-dibenzo[a,c]cycloheptatriene (β_1-VII).—An 8.16-g. sample of β_1-saturated half-ester (β_1-IV) (m.p. 126–127°) was cyclized under the conditions described above to yield 7.0 g. (91%) of solid, m.p. 94–96°, which after three recrystallizations from aqueous ethanol consisted of 5.85 g. (76%) of thin, colorless blades, m.p. 97–97.5°.

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.71; H, 7.30.

The semicarbazone of β_1-VII was obtained as a white powder after six recrystallizations from aqueous ethanol, m.p. 234–236° (dec.).

Anal. Calcd. for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04. Found: C, 65.07; H, 6.96.

α_1-Isomer of Methyl 1,2,3,4,4a,9,10,10a-Octahydro-9-ketophenanthryl-10-acetate (α_1-XIX).—The acid chloride prepared from 1.5 g. (0.0052 mole) of α_1-IV was dissolved in 25 ml. of dry, thiophene-free benzene and was added over a period of one-half hour to a stirred solution of 1.8 ml. (0.016 mole) of anhydrous stannic chloride in 80 ml. of benzene. The reaction mixture was stirred an additional 2.5 hours and was then worked up to give 1.19 g. (85%) of solid, m.p. 62–69°, which upon several recrystallizations from petroleum ether (b.p. 63–69°) consisted of slightly curved, feathery needles, m.p. 75–76°; $\lambda_{max}^{CHCl_3}$ in cm.$^{-1}$ 845, 862, 880, 904, 953, 992, 1036, 1060, 1085, 1097, 1118, 1150, 1170, 1192, 1250, 1272, 1290, 1318, 1345, 1360, 1375, 1415, 1445, 1455, 1480, 1605, 1680, 1720, 2840, 2880, 2990.[22]

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.73; H, 7.21.

Repeated attempts by two methods to prepare a semicarbazone of α_1-XIX failed.

The same keto ester was obtained under the following conditions: (a) aluminum chloride in nitrobenzene (67% yield), (b) aluminum chloride in carbon disulfide (65% yield), (c) aluminum chloride in anhydrous hydrogen fluoride (50% yield), (d) stannic chloride in carbon disulfide (35% yield). From reaction b there was also obtained 13% of the seven-membered keto ester α_1-VII. From reaction d there was also obtained 35% of acid material which was recrystallized three times from solvent-D[19] and was obtained as very small needles, m.p. 113–114°; λ_{max}^{EtOH} (ϵ) 244 mμ (56), 248 (100), 253 (147), 259 (182), 264 (135). This material is probably the ester exchange saturated half-ester, **methyl β-carboxy-β-(2-phenylcyclohexane)-propionate (XVIII).**

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.09; H, 7.41.

β-Carbomethoxy-β-(2-phenylcyclohexane)-propiophenone (XXII).—An aluminum chloride-catalyzed cyclization of the acid chloride from 1.5 g. of α_1-IV carried out in benzene solution for 3 hours at room temperature yielded a neutral oil from which 0.6 g. (35%) of solid could be separated. Recrystallization from petroleum ether (b.p. 63–69°) gave very small needles, m.p. 101–102°; λ_{max}^{EtOH} (ϵ) 242 mμ (9830), 280 (1100).

Anal. Calcd. for $C_{23}H_{26}O_3$: C, 78.82; H, 7.48. Found: C, 78.57; H, 7.19.

β-Carboxy-β-(2-phenylcyclohexane)-propiophenone.—Saponification of the ester described above (XXII) yielded 84% of an oily solid which, after four recrystallizations from solvent-D[19] existed as very small rods, m.p. 177–178°.

Anal. Calcd. for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.60; H, 6.93.

(21) In one experiment a sample of the sodium salt and a sample of the acid chloride were separately hydrolyzed. The sole product in both cases was the starting half ester α_1-IV.

(22) We are indebted to Dr. R. T. Rapala of Armour and Co., Chicago, Ill., for this infrared spectrum obtained on a Baird double beam instrument.

Synthesis of the Acetylamino Compounds

6,7,7a,8,9,10,11,11a-Octahydro-7-carbomethoxy-5H-dibenzo[a,c]cycloheptatriene (α_1-**XI**).—Following the directions of Rosenmund and Karg,[23] a solution of 0.86 g. of α_1-VII in 40 ml. of glacial acetic acid was hydrogenated for 30 minutes in the presence of 0.3 g. of 10% palladium-on-charcoal catalyst and 0.6 ml. of perchloric acid. Removal of the catalyst and concentration of the filtrate yielded the desoxy compound in quantitative amount, and three recrystallizations from aqueous ethanol produced glistening, colorless needles, m.p. 82–82.5°; λ_{max}^{EtOH} (ϵ) 257 mμ (257), 263 (310), 271 (256).

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.82; H, 8.39.

6,7,7a,8,9,10,11,11a-Octahydro-7-carboxy-5H-dibenzo[a,c]cycloheptatriene (α_1-**XII**).—A 1.34-g. sample of the keto acid[6] α_1-VIII was hydrogenated as described above for the keto ester to give 1.1 g. (88%) of a solid, m.p. 199–200°, which after four recrystallizations from aqueous ethanol existed as fine, glistening needles, m.p. 201–202°.

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.36; H, 8.20.

The *p*-**bromophenacyl derivative** of α_1-**XII** was obtained as very fine, colorless needles after several recrystallizations from aqueous ethanol, m.p. 163.5–164.5°.

Anal. Calcd. for $C_{24}H_{25}BrO_3$: C, 65.31; H, 5.71. Found: C, 65.02; H, 5.75.

6,7,7a,8,9,10,11,11a-Octahydro-7-N-acetylamino-5H-dibenzo[a,c]cycloheptatriene (**XIII**).—The acid chloride prepared from 0.50 g. of the desoxy acid (XII) by the oxalyl chloride method was converted to the azide by the "wet procedure" described by Smith.[24] The oily azide, obtained by ether extraction of the reaction mixture, was heated at 80–90° in 20 ml. of xylene until nitrogen evolution ceased (30 minutes). The xylene was removed, the residue was heated with 25 ml. of concd. hydrochloric acid (carbon dioxide evolution), and the reaction mixture was then worked up in the usual fashion to yield 0.1 g. of oily, neutral material and an acid-soluble amine fraction which, without purification, was acetylated with acetic anhydride. The 0.3 g. (57% over-all) of solid so obtained was recrystallized four times from ethanol containing a small amount of water to give clusters of opaque needles, m.p. 175–176°.

Anal. Calcd. for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.18; H, 8.97; N, 5.54.

(23) K. W. Rosenmund and E. Karg, *Ber.*, **75**, 1850 (1942).

(24) P. A. S. Smith, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 387.

ST. LOUIS, MISSOURI

[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, AGRICULTURAL RESEARCH ADMINISTRATION U. S. DEPARTMENT OF AGRICULTURE]

Pellitorine Isomers. II. The Synthesis of N-Isobutyl-*trans*-2,*trans*-4-decadienamide[1,2,3]

BY MARTIN JACOBSON

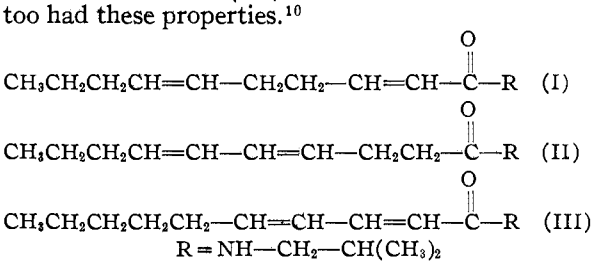
RECEIVED OCTOBER 2, 1952

The synthesis of N-isobutyl-2,4-decadienamide, isomeric with the natural insecticides pellitorine and spilanthol, is described. According to the method of synthesis used, it possesses the *trans* configuration about both double bonds. The compound is both physiologically and insecticidally active. Proof of structure is shown by hydrogenation to N-isobutylcapramide and by oxidation to cleave the double bonds, yielding *n*-caproic, oxalic and N-isobutyloxamic acids.

Since the advancement of structure I for pellitorine,[4] a pungent, insecticidal amide present in pellitory root,[5] the *cis–cis*,[6] *trans–cis*,[7] and *trans–trans*[2] isomers of this structure have been synthesized.[8] Each of these isomers proved to be insecticidally inert, although the *trans–cis* isomer was physiologically active, causing profuse salivation and partial insensitivity of the tongue as shown by natural pellitorine.[4]

Spilanthol (II) is an isomer of pellitorine, being the N-isobutylamide of 4,6-decadienoic acid (configuration about the double bonds unknown). This natural compound also has been reported to be both physiologically and insecticidally active.[9]

It was therefore decided to synthesize N-isobutyl-2,4-decadienamide (III), to determine whether it too had these properties.[10]



The steps employed in this synthesis are shown in the accompanying chart.

n-Caproaldehyde was condensed with malonic acid in the presence of pyridine to give *trans*-2-octenoic acid[11] in 68% yield. This acid has been previously reported by several investigators.[12]

(1) Report of a study made under the Research and Marketing Act of 1946. Article not copyrighted.

(2) This paper was presented before the Division of Organic Chemistry, at the Atlantic City meeting of the American Chemical Society, September 18, 1952 [see *Chem. Eng. News*, **30**, 4131 (1952)].

(3) The first paper in this series is THIS JOURNAL, **72**, 1489 (1950).

(4) M. Jacobson, *ibid.*, **71**, 366 (1949).

(5) J. M. Gulland and G. U. Hopton, *J. Chem. Soc.*, 6 (1930).

(6) R. A. Raphael and F. Sondheimer, *Nature*, **164**, 707 (1949); *J. Chem. Soc.*, 120 (1950).

(7) L. Crombie and S. H. Harper, *Nature*, **164**, 1053 (1949).

(8) After this paper was submitted for publication, Crombie [*Chemistry and Industry*, 1034 (1952)] reported the synthesis of the fourth (*cis–trans*) isomer, which was not identical with natural pellitorine. He considers the latter to be either impure N-isobutyl-*trans*-2,*trans*-4-decadienamide or a stereoisomer thereof.

(9) G. S. Pendse, *et al.*, *Current Sci. (India)*, **14**, 37 (1945); *J. Univ. Bombay*, **15A**, [3] 26 (1946).

(10) After this paper was submitted for publication, Crombie, ref. 7, reported his independent synthesis of this compound (*trans–trans* isomer) and of several of the intermediates reported in the present paper.

(11) The condensation of an aldehyde with malonic acid in the presence of pyridine has been shown to yield the *trans* unsaturated acid. See E. Knoevenagel, *Ber.*, **31**, 2602 (1898); O. Doebner, *ibid.*, **34**, 53 (1901); R. Stoermer and P. Heymann, *ibid.*, **45**, 3099 (1912); K. von Auwers and H. Wissebach, *ibid.*, **56**, 715 (1923); R. A. Letch and R. P. Linstead, *J. Chem. Soc.*, 455 (1932); L. Crombie and S. H. Harper, ref. 7.

(12) M. Bourguel, *Compt. rend.*, **188**, 1494 (1929); G. Bachmann, THIS JOURNAL, **55**, 4279 (1933); A. Seldner, *Am. Perfumer*, **54**, 295 (1949).